UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,625	08/24/2006	Antonello Pietrangelo	LABM-11	2297

7590 07/06/2009

Clifford W Browning
Krieg DeVault
One Indiana Square
Suite 2800
Indianapolis, IN 46204

EXAMINER	
MAIER, LEIGH C	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
07/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,625	PIETRANGELO ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Prosecution

Claims 33-36 have been amended. Claims 1-36 are pending. Any rejection or objection not expressly repeated has been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1-6 and 22-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al (EP 1082963) and Smith et al (Arthritis & Rheum., 1999). Amended claims 33-36 are included in this rejection.

Tamura teaches the preparation of a conjugate of a therapeutic agent for the treatment joint diseases, such as arthritis, and hyaluronic acid (HA) or a salt thereof. The agent may be attached to HA at a hydroxyl group by activating a carboxyl group in the therapeutic agent to prepare an ester linkage. See abstract and paragraphs [0001]; [0057]-[0059]; and [0072]-[0077]. The reference further teaches the preparation of a pharmaceutical composition of the conjugate. The pharmaceutical composition may be prepared in a form suitable for local or parenteral administration. See paragraph [0086]. The reference is silent regarding the concentration and pH of said composition. The reference teaches the general use of these therapeutic agents, see paragraph [0034], but is silent regarding rhein or a derivative thereof.

Smith teaches that diacerhein (diacetylated rhein) has utility for the treatment of osteoarthritis. See abstract.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the product of Tamura by the use of rhein, or a derivative, such as diacerhein, as the therapeutic agent to be conjugated to HA and administer it for the treatment of osteoarthritis with a reasonable expectation of success because this agent is known to be useful for this therapeutic method. In the absence of unexpected results, it would be within the scope of the artisan to optimize the level of esterification of HA in preparing the conjugate through routine experimentation. It would be further within the scope of the artisan to optimize the concentration of the conjugate in a composition, as well as the pH of the composition for this utility through routine experimentation. In administering the conjugate for the treatment of the inflammatory disease, osteoarthritis, the method of "tissue repair" would also be accomplished. With respect to the claims to medical "products" and "devices" the examiner finds no requirements for these products not provided by a pharmaceutical composition, per se.

Applicant's arguments filed March 20, 2009 have been fully considered but they are not persuasive.

Applicant argues that the reference "fails to specifically teach the attachment of a therapeutic agent to HA, [via?] a hydroxyl group, through the activation of a carboxylic group in the therapeutic agent." While the reference may not exemplify such a connection, the clearly suggests this type of bonding, as set forth in the previous Office action. It would be within the scope of the artisan to select an appropriate means of attachment depending on the structure of the therapeutic agent.

Applicant further argues that "at most" the reference discloses metalloproteinase inhibitors and notes that they are "chemically completely different from rhein." Again, the

reference may exemplify the preparation MMP inhibitor conjugates only, the reference is clearly a general teaching with respect to the type of therapeutic agent to be used to prepare conjugates. Many of these are also chemically "completely different" from MMP inhibitors. The criticality is not the structure, per se, but the applicability in the treatment of joint diseases.

Applicant contends that the reference does not address shelf stability, enhanced syringability or synergistic effect of the conjugate. With respect to synergistic effect, Applicant's attention is drawn to paragraph [0019] of Tamura: "… since the synergistic medicinal efficacy of HA and the therapeutic agent for joint diseases can be expected to manifest in the local site, the conjugate can be used as a pharmaceutical composition having improved biological utility." With respect to the other effects mentioned by Applicant, there is no comparative showing that these are not inherent in all HA-drug conjugates.

Applicant discusses at length the perceived deficiencies of Smith, per se. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding the combination of Tamura and Smith, Applicant argues that together the references provide "no guidance at all nor incentive to select any particular site of conjugation on a therapeutic agent for joint diseases, with a specific site on HA, to form a conjugate." The examiner respectfully disagrees. Given the structure of diacetylrhein, the free carboxyl moiety would present itself to one of ordinary skill as the obvious active group to be activated to form a conjugate with HA. This type of linkage is clearly suggested by Tamura.

Finally, Applicant appears to argue that one of ordinary skill would not combine Smith with Tamura because "diacetylrhein lacks inhibitory effect on collagenase activity (metalloproteinase) in OA, and lacks significant effect at later stages in OA." This is not found persuasive because the examiner finds no directive in Tamura or claim limitation that requires the conjugate to have anti-collagenase activity or have significant effect in later stages of OA.

Claims 1-11 and 22-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al (EP 1082963) and Smith et al (Arthritis & Rheum., 1999) in view of Nguyen (US 5,612,321). Amended claims 33-36 are included in this rejection.

Tamura teaches as set forth above. The reference further teaches the purification of conjugates by various methods, including dialysis. See paragraph [0084].

Smith teaches as set forth above.

The references do not teach the preparation of a conjugate comprising reacting the acid chloride of rhein, or derivative or the preparation of said acid chloride.

Nguyen teaches also the preparation of HA-drug conjugates for the treatment of various disorders, such as osteoarthritis. These conjugates are more limited in scope, wherein the therapeutic agent is an antioxidant. See col 4, lines 1-49 and col 7, lines 55-67. The reference further teaches the preparation of an acid chloride of the therapeutic agent (treatment of precursor carboxylic acid with an excess of thionyl chloride in nonpolar aprotic solvent) to be conjugated as well as its reaction with HA. See examples 1 and 6.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use any known synthetic organic technique, such as an acid chloride

reactant for the esterification of HA, to prepare a conjugate of rhein, or derivative thereof. It would be within the scope of the artisan to optimize the relative amounts of the reactants in order to obtain an appropriately modified HA for the utility set forth by Tamura through routine experimentation.

Applicant's arguments filed March 20, 2009 have been fully considered but they are not persuasive.

Applicant first makes piecemeal arguments with respect to Nguyen. This type of argument is addressed above.

With respect to the reaction conditions, Applicant contends that the reference "relates to the grafting of HA to an antioxidant by reaction an ammonium salt of HA with 3,5-di-t-butyl-4-hydroxybenzoyl chloride in the presence of NMP (polar solvent) and ammonium ion, exchanging the resulting product to sodium salt in aqueous solution." (original emphasis) Applicant does not elaborate on this objection. The examiner can only surmise that the underlined portions refer to objectionable differences between the reference and the invention. With respect to "an ammonium salt of HA," it is noted that the claim requires "hyaluronic acid." However, in the absence of criticality in the use of a particular form, it would be within the scope of the artisan to select among acid or salt with a reasonable expectation of success. With respect to "in the presence of NMP (polar solvent)," it is noted that these claims do not recite a limitation with respect to the solvent. Finally, with respect to "ammonium ion, exchanging the resulting product to sodium salt in aqueous solution," the examiner is unable to determine the source of Applicant's objection.

Lastly, Applicant states that Nguyen provides one of ordinary have no incentive to replace the antioxidants by rhein for conjugation with HA. However, Applicant will note that it is Tamura and Smith that together provide the suggestion for making this modification. Nguyen is used merely to teach a synthetic method.

Claims 1-15 and 22-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al (EP 1082963) and Smith et al (Arthritis & Rheum., 1999) in view of Nguyen (US 5,612,321) and Hubbell et al (US 5,834,274). Amended claims 33-36 are included in this rejection.

Tamura and Smith teach as set forth above.

Nguyen teaches as set forth above. The reference does not teach the preparation of the HA conjugate in nonpolar aprotic solvent in the presence of a hydrogen ion acceptor, such as triethylamine. However, the use of these conditions for the acylation of a compound using an acid choride is known in the art. See, for example, Hubbell at examples 1 and 2.

It would be obvious to one having ordinary skill in the art at the time the invention was made to prepare a rhein-HA conjugate, as discussed above. It would be further obvious to select any appropriate reaction conditions, such as those disclosed by Hubbell, for the reaction of the acid chloride reactant with HA with a reasonable expectation of success. With respect to the use of cyclohexane as a solvent for the acylation, it is noted that, given the use of benzene, it would be within the scope of the artisan to select another similar nonpolar, hydrocarbon solvent, such as cyclohexane (hydrogenated benzene) for this reaction. There does not appear to be any criticality in the use of cyclohexane. It would be further obvious to optimize the reaction time through

routine experimentation based on the amount of esterification desired—that is, the amount of the therapeutic agent to be incorporated.

Applicant's arguments filed March 20, 2009 have been fully considered but they are not persuasive.

With respect to Tamura, Smith and Nguyen, Applicant repeats arguments addressed above. Applicant objects to Hubbell as being drawn to "encapsulation and coating technologies that are far remote from the field of the present invention." However, the examiner must determine what is "analogous prior art" for the purpose of analyzing the obviousness of the subject matter at issue. "In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). See also In re Deminski, 796 F.2d 436, 230 USPQ 313 (Fed. Cir. 1986); In re Clay, 966 F.2d 656, 659, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992) ("A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem."); Wang Laboratories Inc. v. Toshiba Corp., 993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993); and State Contracting & Eng 'g Corp. v. Condotte America, Inc., 346 F.3d 1057, 1069, 68 USPQ2d 1481, 1490 (Fed. Cir. 2003) (where the general scope of a reference is outside the pertinent field of endeavor, the reference may be considered analogous art if subject matter disclosed therein is relevant to the particular problem with which the inventor is involved). In the instant case, one of ordinary skill would look to any reference concerned with the particular

synthetic transformation of esterifying an alcohol with an acid chloride. The use of the amine catalyst represents an improvement over the method of Nguyen. Therefore, the examiner maintains that this reference is reasonably pertinent to the instant method.

Claims 1-11 and 16-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al (EP 1082963) and Smith et al (Arthritis & Rheum., 1999) in view of Nguyen (US 5,612,321) and Kuhla et al (US 4,788,187). Amended claims 33-36 are included in this rejection.

Tamura and Smith teach as set forth above.

Nguyen teaches as set forth above. The reference does not teach the preparation of said acid chloride using methylene chloride as the solvent or an inert atmosphere for the reaction. However, these are typical reaction conditions known in the art. See, for example, Kuhla at example 2 (step 1) at col 20.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use any known synthetic organic technique, such as an acid chloride reactant for the esterification of HA, to prepare a conjugate of rhein, or derivative thereof, as set forth above with a reasonable expectation of success. In the absence of unexpected results, it would be within the scope of the artisan to select appropriate reaction conditions for the preparation of the acid chloride, based on those known in the art. It would be further within the scope of the artisan to select any known method, such as dialysis, as suggested by Tamura, for the purification of the HA conjugate.

Applicant's arguments filed March 20, 2009 have been fully considered but they are not persuasive.

Applicant argues that Nguyen does not teach the particularly recited reaction conditions. This was so noted in the previous Office action.

Applicant objects to Kuhla as being drawn to subject matter "far remote from the present invention." The general topic of analogous subject matter is addressed above. Again, with respect to conditions in general synthetic organic chemical reactions, as in the instant case, one of ordinary skill would reasonably look to other methods for the preparation of acid chlorides.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Thursday, and Friday 7:30 to 4:00 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Anna Jiang (571) 272-0627, may be contacted. The fax number for Group 1600, Art Unit 1623 is (571) 273-8300.

Visit the U.S. PTO's site on the World Wide Web at http://**www.uspto.gov**. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more. Information regarding the status of an application may be obtained from the Patent Application Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished application is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

/Leigh C. Maier/
Primary Examiner, Art Unit 1623